

Appl. No. 10/639,076
Amdt. dated November 11, 2004
Reply to Office Action of May 19, 2004

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (currently amended) A peptide ~~which comprises the sequence~~
 - i) ~~comprises the sequence~~
Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂-Cys₂-Glu₃-Arg (SEQ ID NO: 4),
 - ii) ~~competes with SEQ ID NO: 4 for binding FVII/FVIIa in an *in vitro* assay and having wherein~~ between ~~[[1]]zero~~ and ~~[[8]] eight~~ amino acids of SEQ ID NO: 4 ~~are~~ substituted according to the following:
Trp₁ is ~~an amino acid selected from the group consisting of~~ Trp, Phe, Tyr, Leu, Ile, Met, Val ~~and or~~ Ala;
Glu₁ is any amino acid;
Val is ~~an amino acid selected from the group consisting of~~ Val, Trp, Phe, Tyr, Leu, Ile, Met ~~and or~~ Ala;
Leu is ~~an amino acid selected from the group consisting of~~ Leu, Trp, Phe, Tyr, Ile, Met, Val ~~and or~~ Ala;
Trp₂ is ~~amino acid selected from the group consisting of~~ Trp, Phe, Tyr, Leu, Ile, Met, Val ~~and or~~ Ala;
Thr₁ is any amino acid;
Trp₃ is ~~an amino acid selected from the group consisting of~~ Trp, Phe, Tyr, Leu, Ile, Met, Val ~~and or~~ Ala;
Glu₂ is any amino acid;
Thr₂ is any amino acid;
Glu₃ is any amino acid;
Arg is ~~an amino acid selected from the group consisting of~~ Arg, Lys, Leu, Trp, His, Met ~~and or~~ Ile;
and
 - iii) ~~comprises the peptide of ii) binds FVII/FVIIa in an *in vitro* assay.~~

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2. (currently amended) The peptide of claim 1, ~~which:~~
- i) ~~comprises the sequence~~
~~Trp₁, Glu₁, Val, Leu, Cys₁, Trp₂, Thr₁, Trp₃, Glu₂, Thr₂, Cys₂, Glu₃, Arg (SEQ ID NO: 4)~~
- ii) ~~competes with SEQ ID NO: 4 for binding FVII/FVIIa in an in-vitro assay and having wherein between [[1]]zero and [[8]] eight amino acids of SEQ ID NO: 4 are substituted according to the following:~~
- ~~Trp₁ is an amino acid selected from the group consisting of Trp, Phe and Leu;~~
~~Glu₁ is any amino acid;~~
~~Val is an amino acid selected from the group consisting of Val and Ile;~~
~~Leu is an amino acid selected from the group consisting of Leu, Ile, Met, Val and Ala;~~
~~Trp₂ is amino acid selected from the group consisting of Trp, Phe, Tyr, Leu and Met;~~
~~Thr₁ is any amino acid;~~
~~Trp₃ is an amino acid selected from the group consisting of Trp, Phe and Tyr;~~
~~Glu₂ is any amino acid;~~
~~Thr₂ is any amino acid;~~
~~Glu₃ is any amino acid;~~
~~Arg is an amino acid selected from the group consisting of Arg, Lys, Leu and Trp[[:]]~~
- ~~and~~
- iii) ~~comprises the peptide of ii).~~
3. (original) The peptide of claim 2 having an IC₅₀ for FVII/FVIIa of less than 1 μ M.

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4. (original) The peptide of claim 3 having an IC_{50} for FVII/FVIIa of less than 100 nM.
5. (original) The peptide of claim 4 having an IC_{50} for FVII/FVIIa of less than 10 nM.
6. (original) The peptide of claim 5 which binds FVII/FVIIa and inhibits FVIIa activity.
7. (original) The peptide of claim 6 which blocks an activity associated with FVIIa selected from the group consisting of activation of FVII, activation of FIX and activation of FX.
8. (original) The peptide of claim 7 which inhibits activation of FX.
9. (original) The peptide of claim 8 having an IC_{50} for inhibiting FX activation of less than 10 μ M.
10. (original) The peptide of claim 9 having an IC_{50} for inhibiting FX activation of less than 100 nM.
11. (original) The peptide of claim 10 having an IC_{50} for inhibiting FX activation of less than 5 nM.
12. (currently amended) The peptide of claim 11, having the following formula:
 ~~X_1 -Cys₁-X₂-Cys₂-Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₁-Glu₂-Thr₂-Cys₂-Glu₃-Arg-X₄~~
wherein X_1 is absent or is between 1 and 100 amino acids; ~~X_2 is 5 amino acids~~ and X_4 is absent or between 1 and 100 amino acids.

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13. (original) The peptide of claim 12 wherein X_i and X_k are between 1 and 50 amino acids.

14. (original) The peptide of claim 13 wherein X_i and X_k are between 1 and 10 amino acids.

15. (currently amended) The peptide of claim 14 having the formula

~~Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Xaa₆-Cys-Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁-Xaa₁₂-Cys-~~
~~Xaa₁₄-Xaa₁₅-Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂-Cys₂-~~
~~Glu₃-Arg-Xaa₁₆-Xaa₁₇-Xaa₁₈~~, wherein between zero and eight amino acids
are substituted according to the following:

Xaa₁ is an amino acid;

Xaa₂ is an amino acid;

~~Xaa₃ is an amino acid selected from the group consisting of~~ Trp₁ is Trp,

Phe, Leu, Ala, Met ~~and/or~~ Val;

Xaa₄ Glu₁ is an amino acid;

~~Xaa₅ Val is an amino acid selected from the group consisting of~~ Val, Ile,

Ala, Trp ~~and/or~~ Tyr;

~~Xaa₆ Leu is an amino acid selected from the group consisting of~~ Leu, Ile,

Met, Val ~~and/or~~ Ala;

~~Xaa₈ Trp₂ is selected from the group consisting of~~ Trp, Phe, Leu, Met, Ala
~~and/or~~ Val;

Xaa₉ Thr₁ is an amino acid

~~Xaa₁₀ Trp₃ is an amino acid selected from the group consisting of~~ Trp,

Phe, Met ~~and/or~~ Tyr;

Xaa₁₁ Glu₂ is an amino acid;

Xaa₁₂ Thr₂ is an amino acid;

Xaa₁₄ Glu₃ is an amino acid except proline;

~~Xaa₁₅ Arg is an amino acid selected from the group consisting of~~ Arg,

Lys, Leu, Trp, His ~~and/or~~ Met;

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Xaa₁₆ is an amino acid;
Xaa₁₇ is an amino acid; and
Xaa₁₈ is an amino acid.

16. (currently amended) The peptide of claim 15, wherein

Xaa₃ Trp₁ is selected from the group consisting of Trp, Phe, Leu and/or Ala;

Xaa₅ Val is selected from the group consisting of Val, Ile and/or Ala; and

Xaa₈ Trp₂ is selected from the group consisting of Trp, Phe, Leu, Met and/or Ala.

17. (currently amended) The peptide of claim 16, wherein

Xaa₃ Trp₁ is selected from the group consisting of Trp, Phe, and/or Leu;

Xaa₅ Val is selected from the group consisting of Val and/or Ile;

Xaa₆ Leu is selected from the group consisting of Leu, Ile, Met and/or Val;

Xaa₈ Trp₂ is selected from the group consisting of Trp, Phe, Leu and/or Met;

Xaa₁₀ Trp₃ is selected from the group consisting of Trp and Phe; and

Xaa₁₅ Arg is selected from the group consisting of Arg, Lys, Leu and/or Trp.

18. (currently amended) The peptide of claim 17, wherein ~~Xaa₈-Xaa₉-Xaa₁₀-Xaa₁₁-Xaa₁₂-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂~~ is -Trp-Thr-Trp-Glu-Thr- (SEQ ID NO:100).

19. (withdrawn) A method of inhibiting FVIIa activity comprising the step of:

a) contacting FVIIa with a peptide of claim 1 in the presence of tissue factor and under conditions which allow binding of the compound to FVIIa to occur.

20. (withdrawn) A method for selecting a compound which blocks FVII/FVIIa activation of FX comprising the steps of:

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- (1) contacting FVII/FVIIa with a compound of claim 1 in the presence and absence of a candidate molecule under conditions which allow specific binding of the compound of claim 1 to FVII/FVIIa to occur;
 - (2) detecting the amount of specific binding of the compound of claim 1 to FVII/FVIIa that occurs in the presence and absence of the candidate compound wherein the amount of binding in the presence of the candidate compound relative to the amount of binding in the absence of the candidate molecule is indicative of the ability of the candidate compound to block FVII/FVIIa activation of FX.
21. (withdrawn) A method of inhibiting the activation of FX comprising contacting FVII/FVIIa with a compound that prevents the interaction of FVII/FVIIa with a compound of claim 1.
22. (withdrawn) The method of inhibiting the activation of FX of claim 21 comprising contacting FVII/FVIIa with a compound that prevents the interaction of FVII/FVIIa with SEQ ID NO: 4.
23. (withdrawn) The method of claim 22, wherein the contacting occurs *in vivo*.
24. (withdrawn) The method of claim 22, wherein the contacting occurs *in vitro*.
25. (withdrawn) A method of treating a TF/FVIIa mediated disease or disorder in a host in need thereof comprising administering to the host a therapeutically effective amount of a compound of claim 1.
26. (withdrawn) A method of treating a TF/FVIIa mediated disease or disorder in a host in need thereof comprising administering to the host a therapeutically effective amount of the peptide of claim 1.

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27. (original) A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

28. (original) A pharmaceutical composition comprising the peptide of claim 27 and a pharmaceutically acceptable carrier.

29. (original) The composition of claim 28, which is suitable for inhalation.

30. (currently amended) The composition of claim 29, which is dry powder.

31. (currently amended) The composition of claim 29, which is a liquid.

32. (new) A disulfide-constrained peptide comprising the formula

Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂-Cys₂-Xaa-Arg,
wherein between zero and five amino acids are substituted according to the following:

Leu is substituted with Met, Ile, or Val;

Thr₁ is substituted with Ala, Ser, Glu, Gly, Asp, or Gln;

Thr₂ is Gly, Asp, Gln, Ala, Ser, Glu, Thr, Val, or Asn; and

Xaa is any amino acid; and

Arg is Leu, Ser or Trp.

33. (new) A disulfide-constrained peptide of claim 32, wherein the peptide comprises:

Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂-Cys₂-Xaa-Arg,
wherein between zero and five amino acids are substituted according to the following:

Leu is substituted with Met, Ile, or Val;

Thr₁ is substituted with Ala, Ser, Glu, Gly, Asp, or Gln;

Thr₂ is Gly, Asp, Gln, Ala, Ser, Glu, Thr, Val, or Asn; and

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Xaa is any amino acid.

34. (new) A disulfide-constrained peptide of claim 32, wherein the peptide comprises:

SAEWEVLCWTWEGCGSVGLV	(SEQ ID NO:1) TF53;
SEEWEVLCWTWEDCRLEGLE	(SEQ ID NO:2) TF57;
WEVLCWTWEDCER	(SEQ ID NO:3) TF 64
WEVLCWTWETCER	(SEQ ID NO:4) TF 65
WEVVCWTWETCER	(SEQ ID NO:5) TF 66
EWEVLCWTWETCERGE	(SEQ ID NO:17) TF99;
EEWEVLCWTWETCERGED	(SEQ ID NO:18) TF100; or
EEWEVLCWTWETCER	(SEQ ID NO:23) TF183.